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## Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001

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### Abstract

**Background**—A proportion of subjects with symptoms of posttraumatic stress disorder (PTSD) are unresponsive to specialized psychotherapy, but a biological basis for this has not been described. To observe whether differences in cortisol or its metabolites predict or correlate with response to therapy for PTSD symptoms, cortisol and its metabolites were measured from urine samples at pre-treatment, at the conclusion of psychotherapy, and at 3-month follow-up.

**Methods**—28 survivors of the World Trade Center attack on September 11, 2001 seeking psychological treatment for PTSD symptoms received four sessions of either exposure therapy or supportive counseling, followed by up to 10 sessions of prolonged exposure in a specialized PTSD treatment program at a private hospital serving the New York City metropolitan area. 24-hr mean integrated cortisol excretion was assessed by radioimmunoassay (RIA); urinary free cortisol and metabolites cortisone, 5 $\alpha$ -tetrahydrocortisol (5 $\alpha$ -THF), 5 $\beta$ -tetrahydrocortisol, and tetrahydrocortisone were assessed by gas chromatography-mass spectrometry (GCMS); and indices of enzyme activities for 5 $\alpha$ - and 5 $\beta$ -reductase and for the 11 $\beta$ -hydroxysteroid dehydrogenases were derived from the metabolite and glucocorticoid measures.

**Results**—5 $\alpha$ -reductase activity was significantly lower at pre-treatment among non-responders, whereas there were no significant pre-treatment differences between responders and non-responders in any other hormone or metabolite level. In repeated-measures analyses across the three time points,

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### CONTRIBUTORS

Authors Rachel Yehuda, Ph.D. and Linda M. Bierer, M.D. designed the study and wrote the protocol, oversaw data management, collection and analysis and prepared the manuscript. Author Casey Sarapas managed the literature searches, compiled references and composed tables and figures. Author Iouri Makotkine, M.D. was responsible for lab standardization, ensured quality control of biological specimen collection, processing and shipping, and performed urine extraction and cortisol radioimmunoassay. Author Ruth Andrew, Ph.D. performed metabolite assays on GCMS, which was overseen by author Jonathan R. Seckl, M.D., Ph.D. Authors Andrew and Seckl interpreted biological data, performed data analysis and assistant in manuscript preparation.

All authors had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and have approved the final manuscript.

5 $\alpha$ -reductase activity, as well as 5 $\alpha$ -THF and total glucocorticoids, significantly differed between responders and non-responders. For urinary cortisol measured by RIA, there was a significant group  $\times$  time interaction indicating that, although not different at pre-treatment, urinary cortisol levels declined over time in the non-responder group, such that by follow-up, lowered cortisol significantly distinguished non-responders from responders. Indices of 5 $\alpha$ -reductase activity, including 5 $\alpha$ -THF and total glucocorticoids, were significantly negatively correlated with avoidance symptom severity at pre-treatment. At follow-up, indices of 5 $\alpha$ -reductase activity were significantly negatively correlated with severity of all three PTSD symptom clusters and with total PTSD severity scores.

**Conclusion**—Lower 5 $\alpha$ -reductase activity is associated with avoidance severity and predicts non-responsiveness to psychological treatment for PTSD symptomatology. Relatively diminished 5 $\alpha$ -reductase activity may mark a state of primary vulnerability, perhaps via attenuated peripheral catabolism of cortisol resulting in the suppression of hypothalamic-pituitary-adrenal axis responsiveness. Lower cortisol levels appear later in the progression to chronic, treatment-resistant PTSD.

### Keywords

Posttraumatic stress disorder; cortisol; cortisol metabolites; glucocorticoid metabolism; biological markers; psychotherapy; 5 $\alpha$ -reductase; 5 $\alpha$ -tetrahydrocortisol (5 $\alpha$ -THF)

## INTRODUCTION

Although psychotherapeutic interventions accelerate recovery from posttraumatic stress disorder (PTSD), a proportion treated fail to show substantial reduction of symptoms or remission (Ehlers et al., 2003; Sijbrandij et al., 2007; Bryant et al., 2008). To date, however, few psychological (Forbes et al., 2002, 2003a, 2003b) or biological indices (Olf et al., 2007) have been shown to predict or correlate with treatment outcome. Cortisol is associated with normative adaptations to stress. Lower than normal basal cortisol levels have been consistently reported in chronic (>3 months after trauma) PTSD in combat veterans (Mason et al., 1986; Boscarino, 1996; Yehuda et al., 1996), Holocaust survivors (Yehuda et al., 1995; 2007a), victims of chronic child abuse or domestic violence (King et al., 2001; Griffin et al., 2005; Bremner et al., 2007), but are more variable in association with single-incident civilian traumatization (Yehuda, 2006). Furthermore, findings of low cortisol may vary based on sampling methodology (e.g., single plasma or serum samples vs. integrated urine collections), collection times, or participant characteristics (e.g., gender) (Meewisse et al., 2007).

Lower cortisol levels may be a vulnerability trait for PTSD, a notion supported by observations of lower cortisol levels in those “at risk” for PTSD, such as offspring of persons with PTSD (Yehuda et al., 2005a; 2007b). Additionally, low cortisol levels have been reported early after acute trauma in some studies (Yehuda et al., 2005b; Delahanty & Nugent, 2006). However, cortisol levels may show posttraumatic accommodations in those who develop PTSD, as evidenced by a failure to observe consistent reductions several weeks or months following trauma exposure (Hawk et al., 2000; Bonne et al., 2003; Shalev et al., 2008). To date, there has been only one longitudinal study of biological alterations in association with a psychotherapeutic intervention for PTSD (Olf et al., 2007), in addition to a single case report (Kellner et al., 2002).

To address the paucity of longitudinal data on biological alterations in PTSD, we assessed glucocorticoids in 24-hr urine samples in trauma survivors seeking treatment for PTSD and related symptoms in the months following the World Trade Center (WTC) attack on September 11, 2001. Samples were evaluated prior to treatment onset, at the conclusion of psychotherapy, and at three month follow-up. In addition to evaluating urinary cortisol using standard

radioimmunoassay (RIA) procedures, gas chromatography-mass spectrometry (GCMS) was used to estimate urinary-free cortisol (F) as well as the concentration of inactive glucocorticoid metabolites including cortisone (E), 5 $\alpha$ -tetrahydrocortisol (5 $\alpha$ -THF), 5 $\beta$ -tetrahydrocortisol (5 $\beta$ -THF), and tetrahydrocortisone (THE). Quantification of these metabolites allows inferences to be made regarding the activity of enzymes involved in glucocorticoid metabolism by calculating the ratios of respective glucocorticoid metabolites to cortisol.

Specifically, we examined whether changes in 11 $\beta$ -hydroxysteroid dehydrogenases (11 $\beta$ -HSDs) and 5 $\alpha$ - and 5 $\beta$ -reductases were associated with acute and chronic neuroendocrine and symptomatic parameters of PTSD (Seckl, 2008). The two isozymes of 11 $\beta$ -HSD catalyze interconversion of active cortisol and inert cortisone (Seckl and Walker, 2001). 11 $\beta$ -HSD type-1 reduces inert E to active F in liver, fat and brain, resulting in greater intracellular free cortisol (Paterson et al., 2004). Reciprocally, 11 $\beta$ -HSD type-2 rapidly inactivates F to E in distal nephron (Edwards et al., 1998). Cortisol is also catabolized largely in the liver by 5 $\alpha$ - and 5 $\beta$ -reductases (Westerbacka et al., 2003). Variation in these enzymes impacts upon cortisol half-life and thus hypothalamic-pituitary-adrenal (HPA) axis activity (Westerbacka et al., 2003). We hypothesized that cortisol and its metabolism, at least some of which is determined by genetics (Hebbar and Archer, 2007) and early life events (Seckl and Meaney, 2006; Oberlander et al., 2008), would predict and parallel symptomatic recovery in PTSD. Specifically, we predicted that low cortisol levels would be associated with PTSD symptom severity, and would be significantly lower post-treatment in non-responders. Despite these directional hypotheses for cortisol, two-tailed significance tests were used in all analyses.

## METHODS

### Participants

Participants were 28 survivors of the terrorist attack on the WTC in New York City who responded to advertisements for a psychological treatment study, and were drawn from a larger study aimed at investigating the efficacy of a brief course (4 sessions) of prolonged exposure therapy (PE) compared to supportive counseling (SC). After four weeks, participants who did not achieve substantial recovery were offered up to 10 additional sessions of PE. 51 participants began treatment in the larger study; of these, 44 completed the trial (defined as receiving at least four initial sessions, plus additional sessions if responder status had not been achieved following the fourth session). Since the collection of biological samples was optional, only 28 of the 44 completers provided a post-treatment urine sample. These 28 participants comprise the sample included in this study, of whom 14 had initially been randomized to PE and 14 to SC. A brief report describing urinary cortisol and norepinephrine levels at the initial evaluation was published elsewhere (Bierer, et al., 2006).

Recruitment was initiated within three months of 9/11, and closed approximately one year later. Mean duration ( $\pm$ SD) from 9/11 to pre-treatment evaluation was 283 $\pm$ 106 days. Participants were included if they were 18 years or older, reported re-experiencing symptoms and distress related to the WTC attack, and did not meet exclusion criteria. Exclusion criteria were the presence of an Axis I disorder other than PTSD, major depressive disorder (MDD), or anxiety disorder; evidence of current suicidal intent or behavior (3 or 4 on the suicide item of the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) or otherwise assessed as a suicide risk); indication of alcohol or illicit drug abuse or dependence within three months of study; and unwillingness to suspend current psychotherapy. Participants who had been taking stable doses of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) for three or more months (n=9) were not asked to withdraw from medication use, but those using these medications for less than three months, ingesting other psychotropic medications, or ingesting medications that might interfere with the assessment of the HPA axis (e.g., steroids, beta-blockers, indomethacin) were not included. Prior to

treatment initiation, 3 were excluded due to substance abuse or dependence; 2 due to medication exclusions; 2 did not meet the minimum PTSD severity score for inclusion; 2 had excluded psychiatric diagnoses; 1 due to a medical exclusion; and 1 due to having a focal trauma other than 9/11 (and was treated in our clinic but not included for research). After treatment initiation, 2 were discovered to be ineligible (one due to a lapse in alcohol abstinence, and one as it became apparent that symptoms were in response to a trauma prior to 9/11). All subjects signed informed consent for treatment participation, which was offered at no cost; subjects were reimbursed for providing biological samples. The study protocol was reviewed and approved by the institutional review board at the Mount Sinai School of Medicine.

### Study design

An independent evaluation was conducted by a clinical psychologist in order to determine eligibility for the study and to confirm diagnostic status. The Posttraumatic Stress Symptom Scale-Interview (PSS-I) measured the presence and severity of PTSD (Foa et al., 1993). Other psychiatric diagnoses were made using the Structured Clinical Interview for the *DSM-IV-TR* (SCID; Spitzer et al., 1995). The HDRS was administered to assess suicidality and severity of depressive symptoms. Participants also completed the PTSD Symptom Scale-Self Report (PSS-SR) to assess severity of PTSD (Foa et al., 1997). Subjects were advised to schedule urine collections during a 24-hr period anticipated to be relatively quiescent, in order to obtain estimates of 'basal' glucocorticoid production. Collections for female subjects were scheduled during the follicular phase of the menstrual cycle (Symonds et al., 2004). Participants were evaluated by a non-treating (independent) psychologist at the completion of therapy, and again after a three-month naturalistic follow-up.

### Biological measures

Cortisol and its metabolites were measured in batched assays by electron impact GCMS as previously described (Best and Walker, 1997). The limit of sensitivity for the glucocorticoid measures is 2ng; no interferences were observed. Interassay coefficients of variations were <10% for cortisol and metabolites. Figure 1 provides a summary of the biosynthetic pathways related to cortisol metabolism measured in the current study. Total glucocorticoids were calculated as the sum of F and its metabolites E, 5 $\alpha$ -THF, 5 $\beta$ -THF, and THE. 5 $\alpha$ -reductase activity was inferred from the ratio of 5 $\alpha$ -THF/ F, and 5 $\beta$ -reductase activity, similarly from the ratio of 5 $\beta$ -THF/ F. 11 $\beta$ -HSD-2 activity was inferred from the ratio of E/ F; total 11 $\beta$ -HSD activity from the ratio (5 $\alpha$ -THF + 5 $\beta$ -THF)/THE (Palermo et al., 1996). To provide an index of completeness of collection, creatinine concentrations were measured and urine volumes were reviewed. We measured urinary-free cortisol derived from RIA since this measure is often used in the literature. RIA measures of cortisol provide an estimate of total adrenal output, but the antibody used in the procedure can cross-react with cortisol metabolites, and may not provide information about bioactive cortisol levels, (F), as measured by GCMS (Yehuda, 2002).

### Statistical methods

The basic statistical method consisted of a comparison between two groups: those who demonstrated substantial recovery (defined by a score of 10 or less on the PSS-I and no longer meeting diagnostic criteria for PTSD), and those who did not. The psychological ratings and urinary RIA measures of cortisol did not have distributions that were substantially kurtotic. GCMS data were log transformed for all analyses (other than descriptions of percent change), but means and estimated standard errors of means based on pooled groups, and graphics in all cases are based on raw data for descriptive purposes. There were no significant associations between biological measures and age, gender, body mass index (BMI), medication status, presence of comorbid depression, and days since 9/11 at pre-treatment; however, BMI, gender,



and age showed some associations with GCMS measures at subsequent time points and were therefore used as covariates in all analyses of F, glucocorticoid metabolites and enzyme indices.

Repeated measures analysis of covariance (ANCOVA) for pre-treatment, post-treatment and follow-up assessments was used as the principal method of group comparison to assess differences linear trends for biological measures. Bonferroni criteria were applied to urinary cortisol and its metabolites (5 measures) separately from enzyme indices (4 measures) as the latter were derived from the former and therefore were essentially redundant. To identify potential biological predictors and correlates of treatment response, respectively, measures meeting Bonferroni criteria for significance from the repeated measures analyses were further evaluated by ANCOVA at pre-treatment, and subjected to partial correlation analyses with symptom severity measures at pre- and post-treatment and at follow-up.

## RESULTS

### Differences in Demographic and Clinical Characteristics at Pre-treatment

At pre-treatment evaluation (Table 1), PTSD subjects who would subsequently not respond to therapy (non-responders) were significantly older and had a higher BMI than those who would demonstrate a criterion treatment response (responders), but there were no differences in gender or prior trauma exposure. However, after controlling for age, the two groups no longer differed significantly on BMI ( $F=3.14$ ,  $df=1,25$ ,  $ns$ ). For the majority of participants in either group, 9/11 was deemed their worst lifetime traumatic event. There were also no differences in rates of current depression diagnoses, other anxiety disorders, or past substance abuse. Total PTSD and depression severity scores as assessed by clinician ratings were similarly comparable for responders and non-responders at pre-treatment.

At the time of post treatment evaluation, however, there were significant group differences between responders and non-responders in clinician ratings for both PTSD and depression (for PTSD:  $F=17.69$ ,  $df=1,26$ ,  $p<.0005$ ; for HDRS scores:  $F=7.98$ ,  $df=1,26$ ,  $p=.010$ ) that were sustained at follow-up (for PTSD:  $F=37.96$ ,  $df=1,36$ ,  $p<.0005$ ; for HDRS scores:  $F=8.56$ ,  $df=1,26$ ,  $p=.007$ ). Table 2 demonstrates significant effects of time, indicating that improvement occurred in both the responder and non-responder groups; the significant group  $\times$  time interactions indicate that the responders showed significantly greater improvements than did the non-responders (by definition); with the significant group effects for PTSD and depression ratings indicating that, averaged across the three time points, these differences were substantial.

### Treatment effects on biological measures

Repeated measures ANCOVA showed significant group effects for  $5\alpha$ -THF and for total glucocorticoids, which reflects primarily the contribution of  $5\alpha$ -THF. To illustrate the significant contribution of  $5\alpha$ -THF to the level of total glucocorticoids, urinary levels of these metabolites are highly correlated at pre-treatment (partial  $r=.904$ ,  $df=23$ ,  $p<.0005$ ), and almost as highly correlated at post-treatment and follow-up (at both time points, partial  $r=.873$ ,  $df=23$ ,  $p<.0005$ ). These findings indicate a persistent effect of diminished  $5\alpha$ -reduction in the non-responders. Similar, but weaker results were found for  $5\beta$ -THF and THE, indicating lower  $5\beta$ -reduction among the non-responders, but these results did not meet Bonferroni criteria. The findings pertaining to diminished  $5\alpha$ -reduction among non-responders is borne out entirely by repeated measures analyses of the enzyme indices. A significant group effect is noted for  $5\alpha$ -reductase, indicating reduced activity in the non-responders that satisfies Bonferroni considerations, whereas a similar but weaker finding for the  $5\beta$ -reductase index does not. Neither of the  $11\beta$ -HSD enzymes (total or  $11\beta$ -HSD-2) appeared to be altered by trauma focused treatment. Among the glucocorticoids, metabolites and enzyme indices derived from GCMS determinations, there were no significant effects of time, and no significant group  $\times$

time interactions. These findings were not substantially altered by re-analysis with additional covariation for depression and/or medication status.

### Differences in biological measures at pre-treatment

In order to identify predictors of recovery, we next employed univariate ANCOVA to compare pre-treatment values for responders and non-responders for the three biological measures for which a significant effect was found in the repeated measures analyses. Thus, Bonferroni corrections were applied to two metabolite measures (5 $\alpha$ -THF and total glucocorticoids, each at  $\alpha < .025$ ) and to one enzyme index (5 $\alpha$ -reductase,  $\alpha < .05$ ). 5 $\alpha$ -reductase activity was identified as a predictor of treatment response. Non-responders demonstrated significantly reduced 5 $\alpha$ -reductase activity ( $F=6.43$ ,  $df=23$ ,  $p=.019$ ) in comparison to responders (there was greater than 70% lower pre-treatment 5 $\alpha$ -reductase activity among non-responders). However, neither pre-treatment levels of 5 $\alpha$ -THF ( $F=0.15$ ,  $df=23$ , ns) or total glucocorticoids ( $F=1.01$ ,  $df=23$ , ns) distinguished responders from non-responders.

For descriptive purposes, pre-treatment levels of F, glucocorticoid metabolites other than 5 $\alpha$ -THF and enzymes other than 5 $\alpha$ -reductase were compared for non-responders and responders, controlling for age, gender and BMI. There were no significant differences between the treatment responder groups in any of these measures, or in pre-treatment level of RIA-cortisol. These findings, like those of the repeated measures ANCOVAs, were not substantively altered by additional covariation for depression or medication status.

### Findings for RIA Cortisol

The primary outcomes of the present study were F, its metabolites, and glucocorticoid metabolic enzyme indices, as determined by estimating ratios of metabolites assessed by GCMS. Cortisol levels were also assessed by RIA, principally to facilitate comparison of the present results to previous findings pertaining to glucocorticoids in PTSD. At pre-treatment, urinary cortisol measured by RIA was significantly correlated with F ( $r=.694$ ,  $df=23$ ,  $p<.0005$ ) and total glucocorticoids ( $r=.697$ ,  $df=23$ ,  $p<.0005$ ), as well as each of the other glucocorticoid metabolites; for instance, RIA-cortisol was almost as strongly correlated with 5 $\alpha$ -THF ( $r=.637$ ,  $df=23$ ,  $p=.001$ ), and similarly correlated with 5 $\beta$ -THF ( $r=.691$ ,  $df=23$ ,  $p<.0005$ ), as with F.

Repeated measures ANCOVA indicated a significant group  $\times$  time interaction for urinary RIA cortisol ( $F=11.6$ ,  $df=1,26$ ,  $p=.002$ ) in the absence of a main effect of group or time. Though not different at pre-treatment (mean  $\pm$  SE, non-responders:  $51.9 \pm 5.5$ ; responders:  $49.1 \pm 5.5$ ), RIA cortisol levels declined appreciably over time in the non-responder group and increased (less dramatically) in the responder group, such that by the follow-up assessment, the two groups were significantly distinguishable (mean  $\pm$  SE, non-responders:  $37.5 \pm 5.3$ ; responders:  $55.0 \pm 5.3$ ).

### Relationship of glucocorticoid production to treatment response

Examination of the descriptive data provided in Table 2 reveals a consistent overall pattern: glucocorticoid metabolites trend downward among non-responders from pre-treatment to post-treatment, and appear to stabilize or continue to decline from post-treatment to follow-up. This treatment effect is not observed in the enzyme data, where, fundamentally, stable indices are observed overtime, and group differences do not emerge, but are generally apparent at pre-treatment and persist across the three assessments.

The pattern observed for the metabolite data is summarized graphically in Figure 2, which illustrates that the predominant effect overtime for the non-responder group was to show a decline in the production of cortisol and its metabolites, while those who responded to treatment tended to increase production. The figure depicts percent change of group means from pre-

treatment to follow-up in F, E, 5 $\alpha$ -THF, 5 $\beta$ -THF and THE, for the non-responders and responders, respectively. Calculated individually, percent change was negative for the non-responders and positive for the responders in F and every metabolite other than 5 $\alpha$ -THF in which the percent increase among non-responders (35.0%) was only half as great as that for the responders (97.1%), but this difference was not significant ( $F=.83$ ,  $df=22$ , ns), controlling for age, gender, BMI, and pre-treatment 5 $\alpha$ -THF level. Percent change in total glucocorticoids, however, differed significantly between non-responders (-17.0%) and responders (64.2%) ( $F=5.05$ ,  $df=22$ ,  $p=.035$ ), controlling for age, gender, BMI, and the level of total glucocorticoids at pre-treatment.

### Associations between biological and symptom measures at pre-treatment and over time

Only 5 $\alpha$ -THF, and total glucocorticoids, which is highly reflective of the contribution of 5 $\alpha$ -THF, were shown to differentiate treatment responders from non-responders significantly in the repeated measures analyses. Of the enzyme indices, only 5 $\alpha$ -reductase significantly differentiated these groups, but unlike the metabolites, the enzyme activity was significantly reduced among the non-responders at pre-treatment. Each of these three biological measures was evaluated for their association with PTSD symptom ratings at pre-treatment, and at follow-up as indicated in Table 3. Prior to treatment, urinary 5 $\alpha$ -THF was significantly negatively associated with self-ratings for avoidance, as was total glucocorticoids, though somewhat less so. Negative correlations for 5 $\alpha$ -reductase measures with avoidance scores were of similar magnitude prior to and following treatment. At follow-up, when a greater range was apparent for behavioral as well as biological measures as a result of clinical improvements among responders, significant correlations are evident for all three indices of 5 $\alpha$ -reduction (5 $\alpha$ -THF, total glucocorticoids, and 5 $\alpha$ -reductase) across the three behavioral dimensions of PTSD and PTSD total score. All significant partial correlation results shown in Table 3 at pre-treatment and at follow-up for measures of 5 $\alpha$ -reduction meet Bonferroni criteria.

There were only few pre-treatment biological predictors of PTSD symptom severity at follow-up, and all pertained to lower pre-treatment estimated 5 $\alpha$ -reductase activity predicting greater follow-up PTSD symptom severity (i.e., pre-treatment 5 $\alpha$ -reductase activity with follow-up self-rated intrusive symptoms,  $r=-.479$ ,  $df=23$ ,  $p=.018$ , and PTSD total score,  $r=-.407$ ,  $df=23$ ,  $p=.044$ ). Lower pre-treatment self-rated avoidance symptoms correlated negatively with RIA cortisol at pre-treatment ( $r=-.500$ ,  $df=23$ ,  $p=.007$ ) and at follow-up ( $r=-.550$ ,  $df=23$ ,  $p=.041$ ).

For descriptive purposes, similar correlational analyses were evaluated for pre-treatment F, metabolites other than 5 $\alpha$ -THF, and enzymes other than 5 $\alpha$ -reductase. None of these glucocorticoids, metabolites, or enzyme indices was significantly associated with self- or clinician rated PTSD symptom subscales or total score at pre-treatment or follow-up.

## DISCUSSION

This study demonstrates differences in urinary cortisol parameters over time in treatment seeking subjects who were deemed non-responders to psychotherapy for PTSD compared to those who showed full recovery. The findings replicate and extend observations from the only other longitudinal study of cortisol alterations in PTSD before and after cognitive behavioral therapy (CBT), which demonstrated a further decrement in morning plasma cortisol levels post-treatment in non-responders, while those who did respond showed cortisol increases following CBT (Olff et al., 2007). Similar to the current study, plasma cortisol levels at pre-treatment were not significantly different between responders and non-responders, nor did pre-treatment cortisol levels predict treatment outcome. That cortisol levels might change in association with symptom modification is consistent with observations of a relationship between low cortisol levels and high PTSD symptom severity in chronic patients (Baker et al., 1999; Goenjian et al., 2003; Olff et al., 2006a). Interestingly, cortisol levels changed most in



this and the previous longitudinal study in those demonstrating the least change in clinical symptoms, i.e., among subjects showing the least improvement. In a longitudinal case study (Kellner et al., 2002), morning salivary RIA cortisol levels did not show significant decline until the third month following trauma and only began to rise as clinical symptoms showed initial indications of sustained improvement. This, and the results of the current investigation, suggest that cortisol levels may continue to decline as PTSD becomes more chronic or treatment-resistant.

By adding an evaluation of cortisol metabolites to the neuroendocrine assessment in the current study, it was possible to identify 5 $\alpha$ -reductase activity as a putative predictor that differentiated responders from non-responders at the pre-treatment evaluation. Changes in the activity of glucocorticoid metabolic enzymes, and in particular, 5 $\alpha$ -reductase, have been observed in association with extreme stress (Sánchez et al., 2008). We infer that this reflects the 5 $\alpha$ -reductase type 1 isozyme, highly expressed in liver and brain in both genders, since the other isoform, 5 $\alpha$ -reductase type 2 is largely confined to male secondary sexual structures. 5 $\alpha$ -reductase activity is increased in obesity (Livingstone et al., 2000), but lower activity was seen in the treatment-resistant group which had the higher BMI, suggesting that this is not the cause of the differences observed. Diminished 5 $\alpha$ -reductase activity has been associated with cardiovascular risk, the development of metabolic syndrome, as well as other health related risk factors associated with trauma exposure and PTSD (Jakovljevic et al., 2006; Vieweg et al., 2006; Violanti et al., 2006). It is possible that changes in 5 $\alpha$ -reductase occurred early in response to the trauma of the 9/11 attacks. Conversely, insofar as lifespan levels of 5 $\alpha$ -reductase have also been associated with perinatal (developmental) 'programming,' in rodents, it is plausible that the observed differences between responders and non-responders constitute a pretraumatic risk factor that also increased the risk for the development of PTSD, or more refractory PTSD, following 9/11 (Melcangi et al., 1998).

At pre-treatment, indices of diminished 5 $\alpha$ -reductase activity and associated hormonal measures were correlated with avoidance. According to psychological models of PTSD, chronic PTSD results from behavioral and cognitive avoidance of traumatic reminders. The design of the current study, however, does not speak to the origin of lower 5 $\alpha$ -reductase in PTSD. The current findings imply that avoidance may be underpinned by altered cortisol metabolism, specifically by lowered 5 $\alpha$ -reductase, which itself may be a lifelong trait. Interestingly, there is an emerging behavioral literature to support enhanced fear, and anxiety-like behaviors in response to experimentally induced 5 $\alpha$ -reductase inhibition (Frye et al., 2004; Kita et al., 2008; Mann 2006). Mice subjected to prolonged social isolation develop enhanced contextual fear, impaired fear extinction, and emotional hyper-reactivity in temporal association with diminished 5 $\alpha$ -reductase activity in medial prefrontal cortex, hippocampus and basolateral amygdala (Agís-Balboa et al., 2007). Whether, in the present study, lower 5 $\alpha$ -reductase preceded 9/11, was a consequence of exposure, or of the development of PTSD, the finding was associated with PTSD symptom severity and maintenance.

The activities of glucocorticoid metabolic enzymes alter the effective half-life of cortisol and may accordingly influence the HPA axis (Andrew et al., 1998). In the current study, the activities of 5 $\alpha$ -reductase, 5 $\beta$ -reductase and of 11 $\beta$ -HSDs remained stable, even as the overall rate of cortisol production declined. These findings suggest that the factors involved in regulating enzyme activity in PTSD may be distinct from those determining overall cortisol production in the adrenal gland.

In view of the fact that cortisol levels have not been found to change in response to pharmacological intervention in PTSD (Tucker et al., 2004a, 2004b), it is appropriate to consider whether alterations in cortisol levels may reflect alterations in the psychological processes that are altered by psychotherapy – e.g., cognitive appraisal and coping styles. This

would be consistent with the suggestion of Mason et al. (2001) that fluctuations in urinary cortisol excretion over time in combat veterans are mediated by psychological processes and transient stressors. That cortisol treatment may be effective in alleviating symptoms of PTSD (Aerni et al., 2004), or even in preventing the onset of the disorder (Shelling et al., 2006), is consistent with this proposition.

An interpretive challenge for this study is the absence of a non-exposed control group, or a comparably exposed group that did not develop PTSD. All persons studied demonstrated significant enough PTSD symptoms to warrant treatment. Thus, while conclusions about biological predictors and correlates of recovery can be made, the design does not permit inferences regarding measures associated with trauma exposure or resistance to PTSD. Moreover, as subjects were studied within a year of exposure to 9/11, it is likely that at least some of the observed reductions in symptom severity may represent spontaneous recovery rather than treatment response (Kessler et al., 1995).

The study has several limitations. First, the subject number is relatively modest. This limitation is partially offset by having three repeated observations over time with no missing data. A related problem concerns the representativeness of the sample. As stated above, the 28 subjects reported here consist of a subset of a larger group of 44 subjects who completed treatment, who themselves are a subset of an even larger group randomized to psychotherapy after meeting specific inclusion/exclusion criteria. Thus the degree to which persons studied here represent all treatment seekers in the immediate months post-trauma is unclear. This problem is magnified by the fact that those who sought treatment in the first few months after 9/11 were not typical of the larger community with 9/11-related PTSD (Boscarino et al., 2004). Nonetheless, subjects enrolled in treatment who were not included in the present analyses did not differ from the 28 included subjects on any clinical or biological variable of interest at initial evaluation. An additional weakness of the study is the absence of information on cigarette smoking. Tobacco use elevates cortisol levels (Steptoe & Ussher, 2006), and may interact with posttraumatic major depression to affect HPA axis parameters (Olf et al., 2006b). Although the distribution of depression did not differ between responder and non-responder groups, tobacco use may have been a relevant covariate and should be examined in future studies.

Finally, in interpreting the significance of the study it is important to note that the criterion used to differentiate responders from non-responders was extremely conservative, and designed to produce a group of persons who not only no longer met criteria for PTSD post-treatment, but had achieved complete clinical remission (Schnurr et al., 2007). The intervention literature generally employs less stringent criteria for segregating responders from non-responders to examine treatment efficacy. In the present study, however, a psychotherapeutic intervention was exploited to manipulate symptoms to the greatest extent possible so that biological correlates of treatment response and symptoms could be evaluated.

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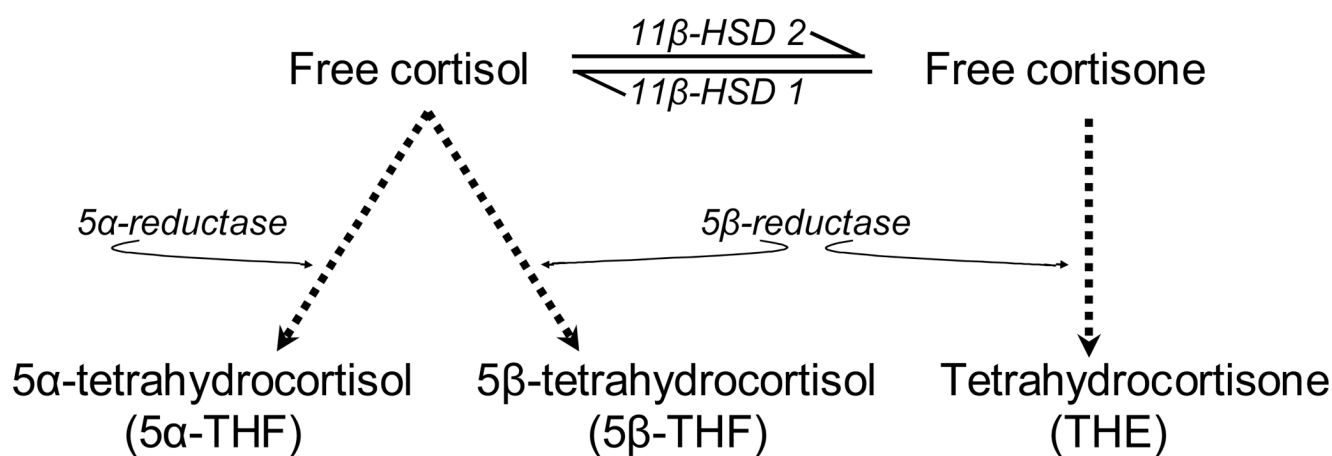
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**Figure 1. Summary of metabolic pathways**

11β-HSD is 11β-hydroxysteroid dehydrogenase. Type 1 oxidizes cortisol to cortisone; Type 2 reduces inert cortisone to cortisol. 5α- and 5β-reductase are the rate limiting enzymes in the conversions of cortisol to 5α-THF and 5β-THF, respectively. 5β-reductase is also rate limiting in the conversion of cortisone to THE.

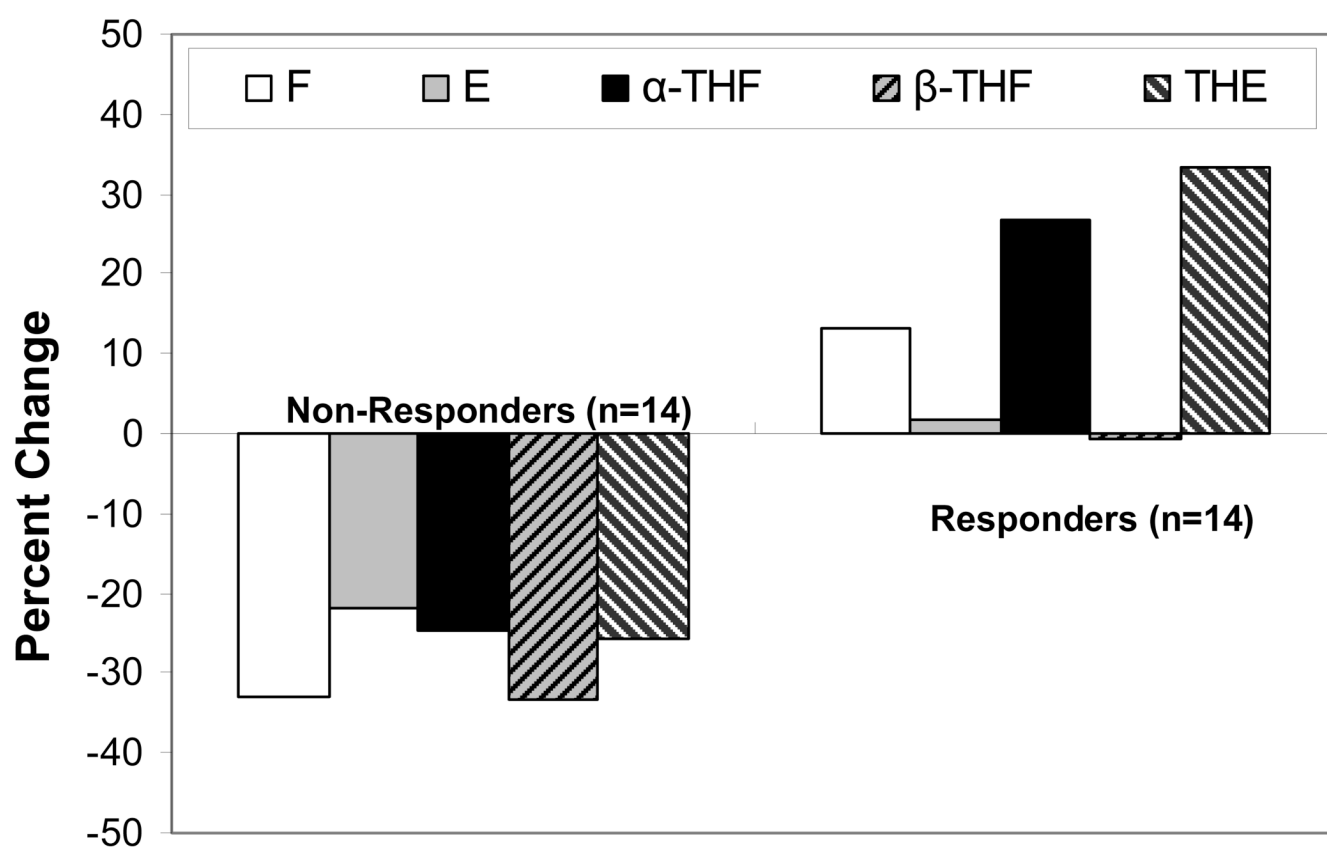


Figure 2. Percent change in means of free cortisol (F) and metabolites from pre-treatment to follow-up for treatment non-responders and responders

Table 1

Demographics, clinical characteristics, and biological measures at pre-treatment

	Non-Responder (n=14)	Responder (n=14)	Statistic	
	<i>M</i> ± <i>SEM</i> or <i>n</i> (%)			
<i>Demographics</i>				
Age	51.4 ± 3.1	40.9 ± 3.1	F= 5.54	df=1,26
Body mass index	29.78 ± 1.30	25.15 ± 1.30	F= 6.37	df=1,26
Gender (% Female)	9 (64%)	6 (43%)	X <sup>2</sup> =1.29	df=1
Days since 9/11	299.9 ± 28.56	266.1 ± 28.56	F= 0.70	df=1,26
<i>Clinical Characteristics</i>				
Posttraumatic stress disorder <sup>b</sup>	13 (93%)	11 (79%)	X <sup>2</sup> =1.17	df=1
Major depressive disorder <sup>c</sup>	7 (50%)	5 (36%)	X <sup>2</sup> =0.58	df=1
Comorbid anxiety disorder <sup>c</sup>	3 (21%)	3 (21%)	X <sup>2</sup> =0	df=1
Past substance abuse <sup>c</sup>	5 (36%)	3 (21%)	X <sup>2</sup> =0.70	df=1
Worst trauma was 9/11 <sup>b</sup>	12 (86%)	12 (86%)	X <sup>2</sup> =0	df=1
Prior other trauma <sup>b</sup>	9 (56%)	7 (44%)	X <sup>2</sup> =0.58	df=1
Clinician-rated PTSD severity <sup>b</sup>				
Intrusive subscale	8.07 ± 0.63	8.07 ± 0.63	F= 0	df=1,26
Avoidance subscale	11.29 ± 1.34	10.86 ± 1.34	F= 0.05	df=1,26
Hyperarousal subscale	11.36 ± 0.83	9.50 ± 0.83	F= 2.50	df=1,26
Total PTSD score	30.71 ± 2.15	28.43 ± 2.15	F= 0.57	df=1,26
Clinician-rated depression <sup>d</sup>	17.57 ± 1.78	15.54 ± 1.85	F= 0.63	df=1,25
Initial condition (%PE) <sup>e</sup>	6 (43%)	8 (57%)	X <sup>2</sup> =0.57	df=1
Prolonged exposure: # sessions	5.57 ± 3.6	3.10 ± 3.3	F= 3.55	df=1,26
PE and/or SC: total # sessions <sup>f</sup>	9.50 ± 3.7	7.00 ± 3.3	F= 3.50	df=1,26

<sup>a</sup> ns p≥.10

<sup>b</sup> Assessed by the Posttraumatic Stress Symptom Scale – Interview (PSS-I)

<sup>c</sup> Assessed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)

<sup>d</sup> Assessed by Hamilton Depression Rating Scale (HDRS)

<sup>e</sup> Initially assigned to prolonged exposure (PE) or supportive counseling (SC)

<sup>f</sup> PE and SC sessions.

Table 2

Comparison of clinical characteristics and biological measures for responders and non-responders.

	Pre-Treatment		Post-Treatment		Follow-up		Repeated Measures ANCOVA <sup>1</sup>	
	NR <sup>2</sup> (M±SEM)	R <sup>2</sup> (M±SEM)	NR (M±SEM)	R (M±SEM)	NR (M±SEM)	R (M±SEM)	Time (F, p)	Grp × Time (F, p)
<b>Clinical characteristics</b>								
PTSD severity <sup>3</sup>	30.7 ± 2.2	28.4 ± 2.2	22.1 ± 2.5	7.1 ± 2.5	23.7 ± 2.1	5.6 ± 2.1	<b>79.8, &lt;.0005</b>	<b>22.5, &lt;.0005</b>
Depression severity <sup>4</sup>	17.6 ± 1.8	15.5 ± 1.9	14.1 ± 2.0	6.4 ± 2.0	12.9 ± 2.0	4.6 ± 2.0	<b>31.6, &lt;.0005</b>	<b>5.20, .031</b>
<b>Urinary hormones &amp; metabolites (µg/24h)</b>								
F	158.6 ± 17.0	110.3 ± 17.0	107.4 ± 18.7	148.7 ± 18.7	112.8 ± 21.2	125.2 ± 21.2	0.11, ns	3.80, (.064)
E	144.5 ± 21.8	119.9 ± 21.8	117.8 ± 29.3	147.7 ± 29.3	104.5 ± 23.7	133.6 ± 23.7	2.20, ns	2.98, (.098)
5α-THF	4196 ± 1593	6582 ± 1593	3048 ± 1182	7039 ± 1182	2652 ± 1478	8583 ± 1478	0.39, ns	0.73, ns
5β-THF	1890 ± 358	2022 ± 358	1012 ± 434	2927 ± 434	1109 ± 324.7	2107 ± 324.7	1.34, ns	2.32, ns
THE	2179 ± 369	2444 ± 369	1837 ± 609	3478 ± 609	1734 ± 625.5	3112 ± 625.5	0.35, ns	2.22, ns
Total glucocorticoids	8568 ± 2060	11279 ± 2060	6122 ± 1768	13740 ± 1768	5713 ± 2095	14061 ± 2095	1.28, ns	2.90, ns
<b>Indices of enzyme activity</b>								
11β-HSD-Total	2.98 ± 0.79	3.80 ± 0.79	3.50 ± 0.77	3.18 ± 0.77	2.78 ± 1.09	5.31 ± 1.09	0.42, ns	0.23, ns
11β-HSD-2	1.00 ± 0.20	1.17 ± 0.20	1.26 ± 0.20	1.10 ± 0.20	0.94 ± 0.16	1.12 ± 0.16	1.81, ns	0.00, ns
5α-reductase	22.89 ± 10.66	65.77 ± 10.66	33.79 ± 10.66	58.37 ± 10.66	16.18 ± 12.26	85.89 ± 12.26	1.47, ns	0.54, ns
5β-reductase	12.37 ± 2.60	20.19 ± 2.60	13.15 ± 3.78	22.14 ± 3.78	9.75 ± 2.32	18.75 ± 2.32	2.31, ns	0.14, ns

<sup>1</sup> For clinical characteristics, ANOVA; for F, metabolites, and enzyme indices, ANCOVA, df=1,23, controlling for age, gender, BMI.

<sup>2</sup> NR = Non-responder (n=14); R = Responder (n=14)

<sup>3</sup> PTSD severity assessed using the Posttraumatic Stress Symptom Inventory - Interview (PSSI); for PSSI, df=1,26.

<sup>4</sup> Depression severity assessed using the Hamilton Depression Rating Scale (HDRS); for the HDRS, df=1,25.

<sup>5</sup> ns=p≥.10

All glucocorticoids and metabolites assessed by gas chromatography-mass spectroscopy (GCMS); F=urinary free cortisol; E=urinary free cortisone; 5α-THF=5α-tetrahydrocortisol; 5β-THF=5β-tetrahydrocortisol; THE=tetrahydrocortisone; Total 11β-HSD=11β-hydroxysteroid dehydrogenase type 1 - inferred from (5α-THF+5β-THF)/THE ratio; 11β-HSD-2=11β-hydroxysteroid dehydrogenase type 2 - inferred from E/F ratio; 5α-reductase - Inferred from 5α-THF/F ratio; 5β-reductase - Inferred from 5β-THF/F ratio. Bold typeface indicates results meeting Bonferroni criteria for statistical significance.



**Table 3**

Relationships of 5 $\alpha$ -reductase and related glucocorticoid metabolites to self-rated PTSD symptoms at pre-treatment and follow-up

<b>a. Pre-Treatment PSSR:Intrusive</b>		<b>Avoidance</b>	<b>Hyperarousal</b>	<b>Total score</b>
	<i>r<sup>a</sup>, p</i>	<i>r, p</i>	<i>r, p</i>	<i>r, p</i>
<i>Pre-treatment biology:</i>				
5 $\alpha$ -THF	.024, ns <sup>b</sup>	<b>-.510, .009</b>	-.092, ns	-.339, (.098)
Total glucocorticoids	-.035, ns	<b>-.473, .017</b>	-.087, ns	-.333, ns
5 $\alpha$ -reductase	-.035, ns	<b>-.444, .026</b>	-.221, ns	-.335, ns
<b>b. Follow-Up PSSR:</b>		<b>Intrusive</b>	<b>Avoidance</b>	<b>Hyperarousal</b>
	<i>r<sup>a</sup>, p</i>	<i>r, p</i>	<i>r, p</i>	<i>r, p</i>
<i>Follow-up biology:</i>				
5 $\alpha$ -THF	<b>-.473, .023</b>	<b>-.581, .004</b>	<b>-.547, .007</b>	<b>-.582, .004</b>
Total glucocorticoids	<b>-.651, .001</b>	<b>-.669, &lt;.0005</b>	<b>-.682, &lt;.0005</b>	<b>-.719, &lt;.0005</b>
5 $\alpha$ -reductase	<b>-.433, .039</b>	<b>-.461, .027</b>	<b>-.501, .015</b>	<b>-.501, .015</b>

<sup>a</sup> Partial correlations, controlling for age, gender and BMI

<sup>b</sup> ns: p $\geq$ .10

5 $\alpha$ -THF=5 $\alpha$ -tetrahydrocortisol (GCMS); Total glucocorticoids=sum of UFF, UFE, 5 $\alpha$ -THF, 5 $\beta$ -THF and THE; 5 $\alpha$ -reductase=Inferred from 5 $\alpha$ -THF/F ratio. Bonferroni considerations applied to metabolites and enzyme measures independently. Bold typeface indicates results meeting Bonferroni criteria for statistical significance.